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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Karimulina 125 mg/ml solution for use in drinking water for chickens, turkeys and pigs [ES]
Karimulina 101.2 mg/ml solution for use in drinking water for chickens, turkeys and pigs [FR]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Tiamulin hydrogen fumarate 125,0 mg
(equivalent to Tiamulin base 101.2 mg)

[FR]
Tiamulin 101.2 mg
(as hydrogen fumarate)
(equivalent to 125.0 mg of Tiamulin hydrogen fumarate)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Propyl parahydroxybenzoate (E-216)	0.1 mg
Methyl parahydroxybenzoate (E218)	0.9 mg
Ethanol (96%)	
Citric acid monohydrate (E330)	
Disodium phosphate dihydrate	
Purified water	

Clear and colourless solution for use in drinking water.

3. CLINICAL INFORMATION

3.1 Target species

Pigs, turkeys (for meat production and for reproduction) and chickens (broilers, chick for replacement, chicken for reproduction and layer hen).

3.2 Indications for use for each target species

Chickens:
Treatment and metaphylaxis of chronic respiratory disease (CRD) and air sacculitis caused by *Mycoplasma gallisepticum*.

The presence of the disease in the group must be established before the product is used.

Turkeys:
Treatment and metaphylaxis of infectious sinusitis and air sacculitis caused by *Mycoplasma gallisepticum* and *Mycoplasma meleagridis*.

The presence of the disease in the group must be established before the product is used.
Pigs:
Treatment of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamuline..
Treatment of pleuropneumonia caused by *Actinobacillus pleuropneumoniae*.
Treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*.
Secondary infection by bacteria such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* can complicate enzootic pneumonia and require specific treatment.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to the excipients.
Do not use in animals that could receive products containing monensin, narasin or salinomycin during or for at least seven days before or after treatment with tiamulin. Severe growth depression or death may result.

See section 3.8 for information regarding interaction between tiamulin and ionophores.

3.4 Special warnings

Acute cases and seriously ill animals with reduced water intake should be treated parenterally.

The water intake of birds should be monitored at frequent intervals during treatment, especially in hot weather, because water intake may be depressed during the administration of tiamulin. This appears to be a concentration-dependent effect and does not appear to have any adverse effect on the overall performance of the birds or efficacy of the veterinary medicinal product. 500 mg tiamulin hydrogen fumarate in 4 litres of water may reduce intake by approximately 10% and 500 mg tiamulin hydrogen fumarate in 2 litres of water by 15% in chickens. In turkeys, this effect is more marked, with approximately a 20% reduction observed and therefore it is recommended not to exceed a concentration of 500 mg tiamulin hydrogen fumarate in 2 litres of the drinking water.

Cross-resistance has been shown between tiamulin and pleuromutilins but also to oxazolidinones, phenicols, streptogramines A and lincosamides notably in *Brachyspira hyodysenteriae* and in *Staphylococcus aureus* in porcine. Use of the product should be carefully considered when susceptibility testing has shown resistance to these antimicrobials because its effectiveness may be reduced.
In some European regions, an increasing proportion of *Brachyspira hyodysenteriae* isolates from clinical cases demonstrate significantly reduced in vitro susceptibility to tiamulin.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

If there is no response to treatment after 5 days, diagnosis should be reviewed.

Not for use for prophylaxis.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

People with known hypersensitivity to tiamulin or to parabens should administer the veterinary medicinal product with caution.

This veterinary medicinal product may cause skin, mucous or ocular irritation.
Direct contact with eyes, skin and mucous membranes should be avoided during the addition of the veterinary medicinal product to the drinking water and the handling of medicated water.
Personal protective equipment consisting of overalls, safety glasses and impervious gloves should be worn when handling or mixing the veterinary medicinal product or the medicated water.

Contaminated clothing should be removed and any splashes on the skin should be washed off immediately.
In case of accidental contact with eyes, rinse immediately with clean water.
Seek medical advice if irritation persists.

Do not smoke, eat or drink when mixing and handling the veterinary medicinal product.
In case of accidental ingestion, seek medical advice immediately and show the label/package leaflet to the physician.

Wash hands after use.

Special precautions for the protection of the environment:

.
The use of this veterinary medicinal product poses a risk to aquatic organisms and to terrestrial plants

3.6 Adverse events

Chicken and turkeys:

Very common (>1 animal / 10 animals treated):	Decrease drinking[1]

[1] See section 3.4

Pigs

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Erythema skin oedema[1]

[1]mild

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system.See the package leaflet for respective contact details. .

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation in swine.

Pregnancy and lactation
Use only according to the benefit/risk assessment by the responsible veterinarian.

Lay
Tiamulin can be used for laying and breeding chicken and turkeys.

3.8 Interaction with other medicinal products and other forms of interaction

Tiamulin has been shown to interact with ionophores such as monensin, salinomycin and narasin and may result in signs indistinguishable from an ionophore toxicosis. Animals should not receive products containing monensin, salinomycin or narasin during or at least 7 days before or after treatment with tiamulin. Severe growth depression, ataxia, paralysis or death may result.

If signs of an interaction do occur, stop both the administration of tiamulin-medicated drinking water and also the administration of ionophore-contaminated feed immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

Concomitant use of tiamulin and the divalent ionophore anticoccidials lasalocid and semduramicin do not appear to cause any interaction, however the concomitant use of maduramicin may lead to a mild to moderate growth depression in chickens. The situation is transient and recovery normally occurs within 3 - 5 days following withdrawal of tiamulin treatment.

3.9 Administration routes and dosage

For use in drinking water.

Chickens (Broilers, chick for replacement, chickens for reproduction and layer hen):

Dose: 25 mg of tiamulin hydrogen fumarate/kg b.w./day (equivalent to 0.2 ml of product/kg b.w./day) for 3-5 days.

Turkeys (for meat production and for reproduction):
Dose: 40 mg of tiamulin hydrogen fumarate/kg b.w./day (equivalent to 0.32 ml of product/kg b.w./day) for 3-5 days.

Pigs:

Treatment of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamuline.

Dose: 8.8 mg of tiamulin hydrogen fumarate/kg b.w./day (equivalent to 0.07 ml of product/kg b.w./day) for 3-5 consecutive days depending on the severity of the infection and/or duration of disease.

Treatment of enzootic pneumonia caused by *M. hyopneumoniae* and treatment of pleuropneumonia caused by *Actinobacillus pleuropneumoniae*.

Dose: 20.0 mg of tiamulin hydrogen fumarate/kg b.w./day (equivalent to 0.16 ml of product/kg b.w./day) for 5 consecutive days.

The weight of the animals should be determined as accurately as possible to avoid underdosing.

If there is no response to treatment after 5 days, diagnosis should be reviewed.

The intake of water depends on the clinical condition of the animals and the time of year. In order to obtain the correct dosage, the concentration of tiamulin may need to be adjusted accordingly.

Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

$$\frac{\text{ml veterinary medicinal product / kg b.w / day} \times \text{mean body weight (kg) of animals to be treated}}{\text{mean daily water intake (litre per animal)}} = \text{ml veterinary medicinal product per litre of drinking water}$$

When large volumes of medicated water have to be prepared, first prepare a concentrated solution and then dilute it to the required final concentration.

Prepare the medicated drinking-water solutions with tiamulin daily.

The medicated water should be the sole source of drinking water during the treatment period.

The use of suitably calibrated measuring equipment is recommended.

Any medicated drinking water remaining from the previous day should be discarded. After the end of the medication period the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Single oral doses of 100 mg tiamulin hydrogen fumarate/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg tiamulin hydrogen fumarate/kg body weight no central nervous system effects were noted except for tranquillisation. At 55 mg tiamulin hydrogen fumarate/kg body weight given daily for 14 days, a transient salivation and slight gastric irritation occurred.
Tiamulin hydrogen fumarate is considered to have an adequate therapeutic index in the pig and a minimum lethal dose has not been established.

Regarding poultry, there is a relatively high therapeutic index with tiamulin hydrogen fumarate and the likelihood of an overdose is considered remote especially as water intake and hence tiamulin hydrogen fumarate intake is reduced if abnormally high concentrations are given.

The oral LD50 for hens is 1090 mg/kg bw and for turkeys 840 mg/kg bw.

The clinical signs of acute toxicity in hens are – vocalisation, clonic cramps and lying in a lateral position, and in turkeys – clonic cramps, lateral or dorsal position, salivation and ptosis.

If signs of intoxication do occur promptly remove the medicated water and replace with fresh water.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

[ES] Administración bajo control o supervisión del veterinario.

3.12 Withdrawal periods

Chickens:
Meat: 6 days
Eggs: Zero days

Turkeys:

Meat: 6 days
Eggs: Not for use in birds producing or intended to produce eggs for human consumption.

Pigs:
Meat: 4 days

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:
QJ01XQ01

4.2 Pharmacodynamics

Tiamulin is bacteriostatic semisynthetic antibiotic belonging to the pleuromutilin group. It acts at the ribosomal level by inhibiting bacterial protein synthesis.

Tiamulin has shown in vitro activity against *Brachyspira hyodysenteriae* and *Mycoplasma spp*. Tiamulin is bacteriostatic at therapeutic concentrations and has been shown to act at the 70S ribosomal level, with the main binding site being the 50S subunit, and possibly the secondary binding site where the 50S and 30S subunits bind. It appears to inhibit microbial protein production by producing biochemically inactive initiation complexes, which prevent elongation of the polypeptide chain.

The mechanisms responsible for the development of resistance to pleuromutilin antibiotics in *Brachyspira spp*. are considered to be based on mutations at the ribosomal binding site. Clinically relevant resistance to tiamulin requires combinations of mutations in the tiamulin binding site. Resistance to tiamulin may be associated with decreased sensitivity to other pleuromutilins.

Furthermore, resistance genes can be located on plasmids or transposons, such as the vga genes and the cfr gene (conferring cross-resistance between pleuromutilins, oxazolidinones, phenicols, streptogramin A, and lincosamides). This type of resistance is transferable between bacteria and bacterial species. The mechanism of antimicrobial resistance varies among bacterial species.

4.3 Pharmacokinetics

Tiamulin is quickly and almost completely absorbed after oral administration.

It concentrates in the lung and liver, where it is rapidly metabolised, resulting in numerous metabolites, most of them biologically inactive.
Excretion is mainly via the bile and kidney.

Chickens
Tiamulin is well absorbed in chickens (70-95%) after oral administration and reaches peak concentrations in 2-4 hours (Tmax 2.85 hours). After a single dose of 50 mg/kg bodyweight, the Cmax was 4.02 µg/ml in serum by microbiological test and after a dose of 25 mg/kg it was 1.86 µg/kg.

Protein binding was approximately 50% (range 45-52%).

Tiamulin is widely distributed throughout the body and has been shown to concentrate in the liver, kidneys, lung (30 times serum level) and eggs. Excretion is mainly via the biliary (55-65%) and renal (15-30%) routes as microbiologically inactive metabolites, being 99% of the dose after 48 hours.

Turkeys
In turkeys, after a single dose of 50 mg/kg bodyweight, the maximum serum levels of tiamulin were 3.02 µg/ml, and 1.46 µg/ml after a single dose of 25 mg/kg. These levels were reached about 2-4 hours after administration of the veterinary medicinal product.

Pig
Tiamulin is well absorbed in pigs after oral administration (approximately 90%).

After an oral dose of 10 and 25 mg of tiamulin per kg of bodyweight, Cmax values were 1.03 µg/ml and 1.82 µg/ml, respectively, and Tmax was 2 hours for pigs.

Tiamulin is excreted mainly via the bile (70-85%), and the remainder is excreted via the kidney (15-30%) as biologically inactive metabolites.

Environmental properties

Tiamulin is very persistent in soil.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: use immediately.
Shelf life after reconstitution according to directions: 24 hours.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

White high-density polyethylene containers containing 1L and 5L product, with a high-density polyethylene screw cap with induction sealing.

Pack sizes:
1 bottle of 1L
1 barrel of 5L

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

The veterinary medicinal product should not enter water courses as Tiamulin may be dangerous for fish and other aquatic organisms.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

LABORATORIOS KARIZOO, S.A.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation:

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).